

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Benny Bang-Andersen, et al.  
Application No.: 10/568,292  
Filed: August 14, 2006  
Group Art Unit: 1624  
Examiner: Emily B. Bernhardt  
Confirmation No. 3519  
For: TRANS-1-(6-CHLORO-3-PHENYLINDAN-1-YL)-3,3-DIMETHYLPIPERAZINE

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

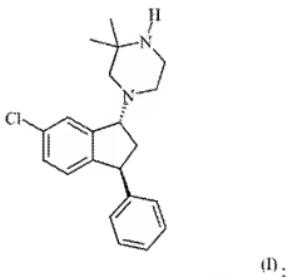
DECLARATION OF KLAUS PETER BØGESØ, D.Sc., UNDER 37 C.F.R. 1.132

I, Klaus Peter Bøgesø, hereby declare as follows:

1. I am a citizen of Denmark, more than twenty-one years of age.
2. I received a Doctor of Science degree in Medicinal Chemistry from Copenhagen University in 1998. Prior to that I received a B.Sc. degree in Chemical Engineering from the Danish Technical University in 1969.
3. I have been employed at H. Lundbeck A/S, the assignee of the present application, for 39 years. During this time, I have held positions as Research Chemist, Head of Medicinal Chemistry, Director of Medicinal Chemistry, Vice President of Medicinal Chemistry, Vice President of Lundbeck Research DK and presently, Vice President of External Affairs.
4. I am the author or co-author of over 50 peer reviewed articles or book chapters, of

which more than 40 are primarily related to medicinal chemistry in connection with dopamine, serotonin and noradrenaline ligands; and I am an inventor or co-inventor of approximately 20 patent families on these subjects.

5. A short version of my curriculum vitae is attached as **Exhibit A**.
6. Benny Bang-Andersen, Henrik Svane, Lars Ole Lyngso, Allan Carsten Dahl, Mark Howells, Klaus Gjervig Jensen, Tomas Mow and I conceived of, and reduced to practice, the invention claimed in the above-identified patent application, as to which we have been named co-inventors.
7. I have reviewed the above-identified patent application, which provides that the invention includes a compound, *trans*-1-((1*R*,3*S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I):



or a pharmaceutically acceptable salt thereof (hereinafter referred to as "Compound I").

8. I have reviewed the Final Office Action mailed February 3 2009, in connection with the above-identified patent application, along with the November 13, 2008 response to the May 13, 2008 Office Action, including the contemporaneously submitted declaration of my co-inventor, Benny Bang-Andersen ("the Bang-Andersen declaration"), pending claims for the application and amended claims being

submitted with a Request for Continued Examination ("RCE") with which my declaration will be contemporaneously submitted. I have reviewed the prior art cited by the Examiner in the office actions – namely, my 1995, *J. Med. Chem.* article describing a series of piperazine ring substituted 1-piperazino-3-arylindans ("the Bøgesø *J. Med. Chem.* article" or "the Bøgesø article") and European patent, EP 0 638 073, of which I am a co-inventor ("the Bøgesø EP patent") (collectively, "the Bøgesø prior art"). I make this Declaration in support of the patentability of the RCE claims in the application.

9. Based on my education and experience in the field of medicinal chemistry of dopamine, serotonin and noradrenaline ligands, I conclude one of ordinary skill in the art in August 2003 – the earliest priority date of the present invention – would have no reasonable expectation of successfully resolving the racemate of Compound I so as to achieve Compound I of the present invention, for the following reasons.

10. The Bøgesø *J. Med. Chem.* article does not provide guidance to one of ordinary skill in the art to arrive at Compound I of the present invention. The Bøgesø article indirectly discloses the racemate of Compound I in Figure 1. It discloses resolution techniques using diastereomeric salt formation. *See* p. 4390.

11. The Bøgesø article teaches that nine *trans* isomers, including compounds 38 (racemate of methylated Compound I), 40 (an *N*-methylated difluoro derivative of Compound I) and 41 (fluorinated Compound I), were successfully resolved using similar procedures to the two specifically described. *See, e.g.*, p. 4390 and Table 2.

12. The Bøgesø *J. Med. Chem.* article, however, fails to suggest, much less teach, that this resolution technique can resolve the racemate of Compound I with a reasonable expectation of successfully obtaining Compound I because it indirectly discloses this racemate and the mere disclosure of the racemate and a resolution technique for compounds of similar structure does not mean that the racemate will be amendable to the resolution technique.

13. Also, with the resolution of these structurally similar compounds, three different resolving agents were used in order to achieve resolution of the racemic compounds. *See, e.g.*, Table 2. The Bøgesø *J. Med. Chem.* article does not teach or suggest which of these three resolving agents will successfully resolve a racemate that is taught; and it certainly does not teach or suggest which of these three resolving agents will successfully resolve a racemate that is indirectly taught, such as the racemate of Compound I. In fact, the Bøgesø article fails to teach or suggest one consistently successful method for resolving these structurally similar compounds.
14. Accordingly, one of ordinary skill in the art could not predict whether the resolution technique described in the Bøgesø *J. Med. Chem.* article would successfully result in Compound I; and without more than what is disclosed in the Bøgesø *J. Med. Chem.* article, one of ordinary skill in the art could not reasonably expect that one of the three resolving agents would successfully resolve the racemate of Compound I.
15. Arguably, the Bøgesø article provides a starting point for obtaining an enantiomer of a racemate of structurally similar compounds. But, this does not mean that one of ordinary skill in the art can predict in advance the result of such pursuit because the pursuit does not have predictable solutions. Plus, just because in the Bøgesø *J. Med. Chem.* article there appears to be a finite number of resolving agents to try, it does not mean there is a finite number of identified, predictable solutions for obtaining Compound I.
16. In fact, an attempt in the fall of 1992 to resolve the racemate of Compound I using a similar procedure as that described in the Bøgesø *J. Med. Chem.* article where the resolving agent was (+)-DTW, which is the same as (+)-DTT in the Bøgesø article (*i.e.*, ditrohoyl-D-tartaric acid) failed.
17. Experiments were conducted in the laboratory at H. Lundbeck A/S, Valby, Denmark, by a technician in my laboratory, Peter Bregnedal, under my direction.

18. A copy of Peter Bregnedal's recordation of his attempted resolution of the racemate of Compound I can be found in **Appendix B**, which provides pages 256-257 of his notebook (Journal 149) at that time. Recordation of the experiment is on page 257, while page 256 is an indication of the time when the experiment was performed.

19. An approximate translation from Danish to English of page 257 provides that:

40 g chlorocompound + 20 g sidechain + 40 g K<sub>2</sub>CO<sub>3</sub> powder in 500 ml MEK [*i.e.*, methylethylketone] is refluxed overnight with agitation. Yield 30 g raw base. 30 g base and 34 g (1 equivalent) D(+)DTW [*i.e.*, D-(+)-ditoluoyltartaricacid] in 500 ml ethylacetate, after 1 week is the compound (at room temperature) completely precipitated. Transformed to the base, the salt crystallizes from EtOH [*i.e.*, ethanol] by addition of 1 equivalent of fumaric acid, recrystallized from CH<sub>3</sub>OH [*i.e.*, methanol] Yield: 18 g. (Lu 31-132-F) pure trans, the last mother liquer is → base

20. The scheme below this entry shows characterization data for the resulting product - namely: Karl Fischer titration for water content, KF 1.1% H<sub>2</sub>O, melting point of 224-226 °C and the result of CHN analyses.

21. Although not directly stated in the notebook entry that the product was the racemate of Compound I (code number Lu 31-132-F) and its resolution by diastereomeric salt formation unsuccessful, this is evidenced by the fact the notebook entry indicated that after a week following addition of the resolving agent, D(+)DTW, the compound was "completely" precipitated (*i.e.* considerably more than the expected half amount if resolution had occurred) and that the precipitate was "pure trans" isomer. It also is evidenced by, for example, that the melting point of the product (224-226 °C) is approximately 30 degrees greater than Compound I (193-196 °C). *See e.g.*, Example 7 of the published application of the present invention.

22. Clearly, the Bøgesø *J. Med. Chem.* article does not provide one of ordinary skill in the art the motivation and/or the means to isolate enantiomeric Compound I from its indirectly disclosed racemate with a reasonable expectation of success.
23. Also, viewing the Bøgesø article together with the Bøgesø EP patent does not provide one of ordinary skill in the art the means to isolate enantiomeric Compound I from its racemate with a reasonable expectation of success. The Bøgesø EP patent alone does not do so as well.
24. Though the Bøgesø EP patent arguably may provide motivation for one skilled in the art to resolve the racemate of Compound I because it teaches that the racemate of Compound I is a preferred compound (see, e.g., [0025]), and “so far” D<sub>1</sub> antagonistic activity lies predominately in one isomer of its racemic compounds (see [0021]), it does not teach a particular resolution technique. It merely teaches that separation of its *trans* isomers into individual optical isomers “may be performed by methods well known in the art” (see [0033]). Without more, this mere suggestion in the Bøgesø EP patent cannot suffice to provide one of ordinary skill in the art the reasonable expectation of success if resolution of the racemate of Compound I was tried.
25. In fact, this mere suggestion could result in undue experimentation. This is indicated by our previous attempt to resolve the racemate of Compound I (see paragraphs 16-21), as well as our attempts to resolve similarly structured compounds by a similar method as that described in the Bøgesø *J. Med. Chem.* article.
26. For example, in the case of the preparation of the enantiomers of compound 40 disclosed in the Bøgesø *J. Med. Chem.* article, direct resolution of compound 40 itself failed, while the secondary amine here could be resolved and the enantiomers could then be methylated to provide the enantiomers of compound 40. Yet, the racemate of Compound I, which also is a secondary amine, could not be resolved by a similar method. See paragraphs 16-21.
27. A copy of Peter Bregnedal’s recordation of his attempted direct resolution of the racemate of compound 40 can be found in **Appendix C**, which provides pages 224-225 of his notebook (Journal 149) at that time. His successful resolution of the

secondary amine of compound 40 before methylation to compound 40 is described in the Bøgesø article. See e.g., p. 4390, col. 2, paragraph 2.

28. An approximate translation from Danish to English of pages 224-225 provides that:

Page 224:

30 g of chloroderivative + 20 g sidechain + 30 g K<sub>2</sub>CO<sub>3</sub> powder is refluxed overnight with stirring. Evaporated on a Rotavapor whereupon water and ether are added. The base is purified by extraction with 1 N CH<sub>3</sub>SO<sub>3</sub>H [followed by liberation of the base again], yield 19 g raw base.

19 g base + 20 ml 30% HCHO + 20ml 99% HCOOH is warmed on a steam bath for 1 hour, the CO<sub>2</sub> generation stops. The base is purified with 1 N CH<sub>3</sub>SO<sub>3</sub>H [see comment above] yield 20 g raw base, NMR ~11% cis [isomer].

Dissolved in 250 ml ethylacetate + 50 ml acetone whereupon 12 g of maleic acid are added, the maleate crys[allizes] 29 g mp. 154-6 °C, converted to the base 15 g dissolved in 250 ml ethylacetate + 50 ml acetone added 15 g (1 equivalent) D(+) DBW [*i.e.*, dibenzoyl-D-tartaric acid], left for 4 hours at room temperature, crystals filtered, washed with ethylacetate. Yield 12.7 g mp. 129-30 °C Yield 12.5 g. Dissolved in 100ml acetone, evaporated, the oil dissolved in 200 ml EtAc [*i.e.*, ethylacetate] → 9 g mp. 129-30 °C.

Page 225:

The mother liquor transformed to the base → 7 g base. Dissolved in 250 ml ethylacetate + 50 ml acetone, added 7 g L(-) DBW [*i.e.*, dibenzoyl-L-tartaric acid], left overnight → 10.5 g mp 129-30,5°C. Dissolved in 100 ml acetone, evaporated, the oil dissolved in 200 ml EtAc [*i.e.*, ethylacetate] → 8 g mp. 129-30 °C.

Converted to the base

I 4 g base [α] -5.1° c=0.5 CH<sub>3</sub>OH

II 4 g base [α] +5.2° c=0.5 CH<sub>3</sub>OH

The hydrochlorides cryst[allizes] from ethylacetate/acetone.

Recrystallized from acetone, no [optical] rotation of the hydrochlorides

29. Although a small rotation was observed with the bases (from DBT salts showing no increase in melting point upon recrystallization) the resulting hydrochlorides are racemic, so the bases must have had a very small enantiomeric excess.
30. This shows the unpredictability of which approach will work in the individual case, resulting very often in undue experimentation.
31. Other examples can be found in my paper in *J. Med. Chem.*, 1993, 36, 2761-2770. Here it is described how direct resolution of a number of the compounds failed and instead, a number of intermediates had to be resolved and then subsequently through several steps were transformed into the desired enantiomers. These compounds are structurally similar to Compound I and its racemate, *i.e.*, the compounds are *trans*-piperazino3-phenylindan derivatives like Compound I and its racemate.
32. Consequently, even after the earliest priority of the Bøgesø EP patent (*i.e.*, April 1992), one skilled in the art could not reasonably expect to successfully resolve the racemate of Compound I. As a result, the Bøgesø EP patent's disclosure is simply too general as to a resolution method to provide meaningful guidance that would lead one of ordinary skill in the art to the claimed Compound I of the present invention.
33. Additionally, it was after the earliest priority of the Bøgesø EP patent that compound 38 of the Bøgesø *J. Med. Chem.* article (*i.e.*, racemate of methylated Compound I) was successfully resolved into its enantiomers. This resolution was successfully performed 23 August 1993. *See Appendix D* for a copy of the experiment's recordation in Peter Bregnedal's notebook, Journal 174, p. 07 (see upper left for date: 23/8-93, and upper right for notebook and page numbers: 174/07). This successful preparation of the enantiomers of compound 38 was subsequently disclosed in the Bøgesø *J. Med. Chem.* article. *See, e.g.*, p. 4390 and Table 2.
34. An approximate translation from Danish to English of page 07 provides that:

12 g of trans fumarate (149/257) → base, heated for 1 hour with 10 ml HCOOH, 98% + 10 ml 37% HCHO. CO<sub>2</sub> generation stops. The base is liberated, yield 8 g base. (-)DTW cryst[allizes] [meaning the salt with (-)-ditoluoyltartaric acid] from 500 ml EtOH, recryst[allized] from 1 L EtOH with 200 ml CH<sub>3</sub>OH added → 3g (I) NMR: ~14% of the other enantiomer. The mother liquor → base, 5.5 g dissolved in 500 ml EtOH, 1 equivalent (+)DTW [*i.e.*, (+)-ditoluoyltartaric acid] is added, filtered next day. Recryst[allized] from 250 ml of CH<sub>3</sub>OH → 3 g (+)DTW salt (II), looks very pure on NMR. Bases [produced from the DTW salts of I and II] are dissolved in 50 ml n-propanol + 1 equivalent fumaric acid.

I 1.3 g base → 1.25g Mp 195.5-97 °C. [α]: +22.2° c=0.5. CH<sub>3</sub>OH.

II 1.3 g base → 1.15g Mp 196-7 °C. [α]: -22.0° c=0.5. CH<sub>3</sub>OH.

35. The schemes below this entry show CHN analyses data for the resulting two enantiomers.
36. This further shows the unpredictability of which approach will work in the individual case, resulting very often in undue experimentation. Here, direct resolution of a methylated tertiary amine was successful, unlike for the methylated tertiary amine, compound 40, as previously stated. *See e.g.*, paragraph 26.
37. Thus, the Bøgesø prior art alone or combined fails to provide one of ordinary skill in the art a means to resolve the racemate of Compound I with a reasonable expectation of success.
38. Without a doubt, at the time of the present invention, the Bøgesø prior art fails in this regard. At that time, one of ordinary skill in the art would not have a reasonable expectation of successfully resolving the racemate of Compound I.
39. At that time, it was not predictable that the racemate of Compound I could be resolved, let alone by diastereomeric salt formation. Indeed, there was no reasonable expectation of successfully obtaining it in this manner without more than routine experimentation because of our prior failed attempt and our general experience with

the resolution of compounds of this type – namely, piperazino-3-arylindans. *See* paragraphs 15-34.

40. In fact, in directing internal resources to finding a way to resolve the racemate of Compound I, it was found that the technique of chiral chromatography could for the first time successfully provide claimed Compound I, as disclosed in the present invention. *See, e.g., [0030]-[0040]* of the published application of the present invention.

41. Also, Compound I in comparison with the prior art compounds has a property with respect to CYP2D6 inhibition that is surprising, unexpected and unpredictable over the prior art Compounds A-H. *See, for example, the submitted declarations of my co-inventors, Benny Bang-Andersen and Klaus Gjervig Jensen, with whose statements with respect to this property I concur.*

42. In summary, the Bøgesø prior art discussed above relates to structurally similar *trans* isomers of the claimed Compound I. The Bøgesø prior art generally discloses diastereomeric salt formation as being a possible means for obtaining the optical isomers of its *trans* isomers. But, this general disclosure is such that its teachings offer little true guidance for one ordinarily skilled in the art so as to expect s/he could successfully obtain optical isomer that is claimed Compound I. In fact, one of ordinary skill in the art could not predict which particular approach of diastereomeric salt formation would be successful in resolving a racemate of this type of compound. This is shown by the Bøgesø prior art itself as in the resolution of compounds 38 and 40, and our general experience with the resolution of piperazino-3-arylindans, as previously discussed. When considering claimed Compound I in view of the prior art, one of ordinary skill in the art would thus conclude that the diastereomeric salt formation resolution techniques disclosed could not predictably and effectively, with a reasonable expectation, resolve the racemate of Compound I because they were without guidance as to a consistently successful method for resolving these structurally similar compounds, offering rather mere suggestions that required more than routine experimentation.

43. Because of the foregoing, Compound 1 of the present invention is not obvious in view of the Bøgesø prior art.

44. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Date

*3 March 2010*

*Klaus Peter Bøgesø, D.Sc.*

## Exhibit A

### CURRICULUM VITAE, KLAUS PETER BØGESØ, D.Sc. - SHORT VERSION

Name: Bøgesø, Klaus Peter

Address: Kirstineparken 21; DK - 2970 Hørsholm, Denmark

Born: 8 February 1947 in Copenhagen, Denmark

#### Education

1969: Bachelor of Engineering (Chemistry) Danish Academy of Engineering

1998: D.Sc (Pharmacy/Medicinal Chemistry) Royal Danish School of Pharmacy

#### Employment

Oct 2008-: Vice President, External Affairs-

2006-2008: Vice President, Lundbeck Research DK, H. Lundbeck A/S

1999-2006: Vice President, Medicinal Chemistry Research, H. Lundbeck A/S

1986-99: Director of Medicinal Chemistry, Medicinal Chemistry Research, H. Lundbeck A/S

1985-86: Head, Dept. of Medicinal Chemistry, H. Lundbeck A/S

1971-85: Research chemist, Dept. of Medicinal Chemistry, H. Lundbeck A/S

1970: Analytical Chemical Laboratory, the Civil Defence

1969-70: The Danish Civil Defence, trained Section Leader II of the Reserve

#### Short summary of research

The research activities of Klaus P. Bøgesø have focused on drug design and development within psychiatric and neurologic diseases such as schizophrenia, depression, anxiety, Alzheimer's disease, Parkinson's disease and epilepsy. Primary targets have been dopamine and serotonin receptors and transporters, muscarinic receptors and glutamate receptors. Klaus P. Bøgesø is inventor of the selective serotonin reuptake inhibitors citalopram (cipramil, celexa) and its active enantiomer escitalopram (cipralex, lexapro), which both have attained super-blockbuster status. Within schizophrenia, his research has led to the antipsychotic drug, sertindole; as well as another antipsychotic, tefludazine, and the 5-HT<sub>2A/2C</sub> antagonist, irindalone. The latter two were discontinued during clinical development. His muscarinic compound, alvameline, was selected from a series of muscarinic agonists and reached phase II clinical trials for

Alzheimer's disease. The differential action of stereoisomers of chiral drugs has been a focus area in many of his research projects, as well as a main topic in several publications, including his doctoral thesis. Current research includes the next generation of new antidepressant and antipsychotic drugs, as well as several neurological research projects.

### **Publications & Presentations**

Author/co-author of 54 scientific publications

Author/co-author of 27 posters and oral communications/presentations

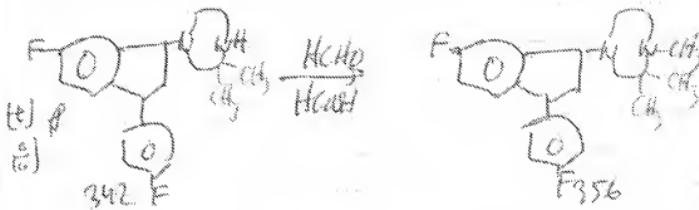
Invited speaker/chairman at 78 symposia, congress, conferences and university courses

### **Patents**

Inventor/co-inventor of 26 patent families

Attempted resolution of the racemate of Compound I  
(pages 256-257 of notebook Journal 149, ~ Oct. 28, 1992)

28/10-92



15, I (40/248) + 5 ml HCl/H<sub>2</sub>O + 5 ml H<sub>2</sub>O, vann  
på dampbad i 1 time. En vilt blikkning. En ej hörts.  
Baserat på förföljande räkning, vitt 63% bär.  
15, II som är procedur över I → 3, 3, bär  
Monofluoracetanhydrid och ethyl acetat vitt blikning  
efter brygning sju veckor. Den bärstaf 10% (2) v. 20 ml Et<sub>2</sub>O och  
1.03 } de kommer inte att blikka  
1.23 }

## APPENDIX B

Attempted resolution  
of the racemate  
of Compound I  
(pages 256-257  
of notebook Journal 149,  
- Oct. 28, 1992)



(808.57) 403.41

Mol. Wt. 403.025



261.89

114

333.45

1/2 chl. benz + 1/2 mde heptane 1/2 Et<sub>2</sub>O + Et<sub>3</sub>N = 50 ml. Et<sub>3</sub>N  
affinie. water over under stirring. 1/2 h. 30<sub>o</sub> g. bottom

1/2 benz + 34. (1/2) 0.6 DTR; 50 ml. Et<sub>3</sub>N reacted,  
aff. 1/2 g. a stofft (valskartap) faldet fald. handigt ut.  
Gedryns 1/2 benz, meddelit fys. Et<sub>3</sub>N var H<sub>2</sub>O-trap. af  
paa fyrhun nys, vandet. af 1/2 Et<sub>2</sub>O + 1/2. Et<sub>3</sub>N, af  
den mde. Et<sub>3</sub>N had. > benz.

	N	C	H
water.	695	6847	676
bottom.	7.14	6843	678

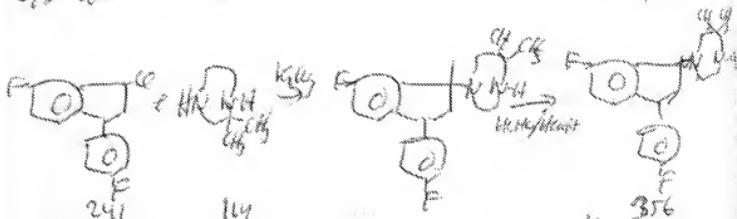
147/224

## APPENDIX C

**Attempted direct resolution of the racemate of compound 40  
(pages 224-225, notebook Journal 149, March 16, 1992)**

186

149/197



3<sup>2</sup>, akkufast + 2<sup>2</sup>, nio hældt Bez kig, gule refleks røde  
øre under omkring. Indlængen på øretoppe, blæsletter hæ-  
ftet. Børn overfaldet med 100% soft, sub 1<sup>2</sup>, 1 bue.  
19<sup>2</sup>, base + 2<sup>2</sup> til 3<sup>2</sup> til 4<sup>2</sup> med 75% hard (væske på dag-  
bæl: 1 bue, 10 gredsklinger, optøse. Børn overfaldet med  
100% soft, sub 2<sup>2</sup> i 1 bue, 10%: 20% i 2<sup>2</sup>.

Ophrys 250 ml ethyl acetate + 50 ml acetone treated 13  
 min (Bünger, mole at 100% 29, 240; 174.6% on column  
 11 base 15% Ophrys 250 ml ethyl acetate + 50 ml acetone treated  
 for 15 min (Bünger) 100% DBW, benzene + 4 times acetone  
 hydrolyzed 100% for 10 min with ethyl acetate. 100% 12.7% 240;  
 179.30% 240; 171.5% Ophrys 100 ml acetone, 100% 240;  
 100% Ophrys 240 ml EAC  $\rightarrow$  7, 240; 179.30% 240

Attempted direct resolution of the racemate of compound 40  
(pages 224-225, notebook Journal 149, March 16, 1992)

1.  $\text{LiAlD}_4$  in  $\text{CH}_2\text{Cl}_2$   $\rightarrow$   $\text{D}_2\text{O}$   $\text{H}_2\text{O}$   $\text{O}_2$   $\text{CH}_2\text{Cl}_2$  250  $\text{mL}$   $\text{diluted}$   
500  $\text{mL}$   $\text{water}$ , stirring  $\text{D}_2\text{O}$  100  $\text{mL}$  (heat and stirrer  
 $\rightarrow$  105, 90°; 125-305. - Optima: 100  $\text{mL}$   $\text{water}$ , 1 ml  $\text{diluted}$   
dien optima: 200  $\text{mL}$   $\text{EtAC}$   $\rightarrow$  8, 90°; 125-30°

On  $\text{D}_2\text{O}$   $\text{H}_2\text{O}$

I 4,5  $\text{H}_2$   $\text{base}$  (0)  $\pm 5,1^\circ$   $\epsilon = 0,5$   $\text{CH}_2\text{Cl}_2$

II 3,7  $\text{H}_2$   $\text{base}$  (0)  $\pm 5,2^\circ$   $\epsilon = 0,5$   $\text{CH}_2\text{Cl}_2$

Hydrochloride salt of ethyl acetate/Proton, crystall. of  
Acetone, hydrochloride. dryer opt.

## APPENDIX D

Resolution of compound 38  
(page 07, notebook Journal 174, August 8, 1993)

L 31-128-F, CH<sub>2</sub>

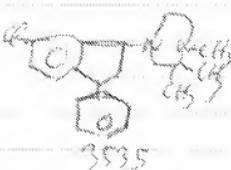
L 31-130-F-102174/07

W.H. (.)



248.77

112/252 X



By turns ferment (148/357) → brown, viscous. 16 hr and  
heat bath, 70°C + 1000 rpm. 100 ml working volume.  
Brown residue, 40%: 1.33 g. 1/2 liter bath of 50 ml each, each  
of 1.0 ml of 200 ml CH<sub>2</sub>Cl<sub>2</sub> → 3.51 (1) NMR: v 142 cm<sub>1</sub> carbon stretching  
infrared → brown, 55%: 50 ml heat bath 100°C 1/2 hr  
brown, 50%: 50 ml heat bath of 250 ml CH<sub>2</sub>Cl<sub>2</sub> → 3.49 (1) NMR: v 142 cm<sub>1</sub> carbon stretching  
infrared, brown, 50%: 50 ml heat bath 100°C 1/2 hr  
I 13C NMR → 1.25, 5.49; 19.5, 47.2, 50.2, 52.2, 54.5, 63.0, 65.0  
II 13C NMR → 1.15, 5.49; 19.6, 47.2, 50.2, 52.0, 54.5, 63.0, 65.0

R.

	N	O	H
800ppm	553	66.19	66.5
Fluorine	6.15	66.57	66.6

	N	O	H
800ppm	5.35	66.29	66.5
Fluorine	6.21	66.30	66.74